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14. ABSTRACT

A small, lightweight microdevice has been developed for activity-dependent stimulation (ADS) and successfully tested for functionality in both anesthetized and ambulatory rats. Further, in semi-chronic experiments in rats with TBI using this microsystem, an unprecedented, potent effect of ADS on motor performance has been demonstrated, as compared to control rats (injured but no microdevice) and open-loop stimulation (OLS) rats. Specifically, open-loop stimulation does result in some recovery after injury, but ADS is significantly more efficacious, resulting in recovery to normal ranges of performance within 2 weeks after injury.

15. SUBJECT TERMS
Anatomical rewiring; Implantable microsystem; Neuroplasticity; Rehabilitation; Traumatic brain injury

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A Brain-Machine-Brain Interface for Rewiring of Cortical Circuitry after Traumatic Brain Injury

Award Number W81XWH-10-1-0742
Randolph J. Nudo, PhD
Annual Report
December 2013

INTRODUCTION:

The goal of this project is to use an implantable brain-machine-brain interface to enhance behavioral recovery after traumatic brain injury by reshaping long-range intracortical connectivity patterns. We hypothesize that artificial synchronous activation of distant cortical locations will encourage spontaneously sprouting axons to migrate toward and terminate in the coupled region, and that such directed sprouting can aid in functional recovery.

BODY:

Substantial progress has been made in demonstrating proof-of-concept for our approach in a rodent model of traumatic brain injury. The Tasks at Kansas University Medical Center comprise the neurobiology components of the collaborative project with investigators at Case Western Reserve University who are performing the electronics and microsystem packaging components. As described in our Year 2 annual report, we submitted our findings, showing rapid recovery of motor abilities in rats implanted with the microdevice, to the journal, *Nature.* The manuscript received favorable reviews, and revisions were requested to provide further evidence, either neurophysiological or neuroanatomical, of enhanced connectivity (no additional studies in new animals required for this analysis). While initially (beginning of Year 3) we thought that this analysis could be completed in a few weeks, it required development of in-depth spike-timing algorithms to extract the data that the reviewers wanted to see. This process was tedious and required several months of work by a graduate student and research analyst. However, the requested changes allowed us to demonstrate functional connectivity in a direct way, and this has yielded very novel and important results. These results were submitted in a revised manuscript to *Nature*, but the paper was ultimately not accepted. We then added additional analyses to further strengthen the argument regarding the underlying functional connectivity that is modulated by activity-dependent stimulation, and submitted the paper to *The Proceedings of the National Academy of Science* (PNAS), where it was accepted. As the date of acceptance is in the first quarter of Year 4, we will provide further details, including the complete paper, in the Year 4, Q1 report.

The algorithms developed during the course of the manuscript revision have proved to be very enlightening. During Year 3, we revisited our Year 1 parameter optimization experiments that were proposed in acute, anesthetized rat preparations. These studies (requiring no new animals or modification of approved procedures) yielded new information on the rapidity and specificity of activity-dependent stimulation that will help guide the further development of this novel approach.

Finally, we worked with the engineering group at Case Western Reserve University to progress in the design of the primate microdevice. We also initiated pilot studies in non-human primates required by our local IACUC before proceeding with the full primate series. These pilot studies are funded by internal KUMC sources, and thus, not subject to approval by ACURO. The full primate series has received full ACURO approval.

In the text that follows, we first summarize the previous and new results of our in-vivo proof-of-concept study, new results from studies that were part of Year 1 tasks and then address progress toward each of the Year 2-3 tasks.

Manuscript in press in PNAS: Restoration of function after brain damage using a neural prosthesis (Complete main body of manuscript is included in the appendix.)

Authors: David J. Guggenmos, Meysam Azin, Scott Barbay, Jonathan D. Mahnken, Caleb Dunham, Pedram Mohseni, Randolph J. Nudo

Summary: Neural interface systems are becoming increasingly more feasible for brain repair strategies. This paper tests the hypothesis that recovery after brain injury can be facilitated by a neural prosthesis serving as a communication link between distant locations in the cerebral cortex. The primary motor area in the cerebral cortex was injured in a rat model of focal brain injury, disrupting communication between motor and somatosensory areas and resulting in impaired reaching and grasping abilities. After implantation of microelectrodes in cerebral cortex, a neural prosthesis discriminated action potentials (spikes) in premotor cortex that triggered electrical stimulation in somatosensory cortex continuously over the subsequent weeks. Within one week, while receiving spike-triggered stimulation, rats showed substantially improved reaching and grasping functions that were indistinguishable from pre-lesion levels by two weeks. Post-hoc analysis of the spikes evoked by the stimulation provides compelling evidence that the neural prosthesis enhanced functional connectivity between the two target areas. This proof-of-concept study demonstrates that neural interface systems can be used effectively to functionally bridge damaged neural pathways and promote recovery after brain injury.

Progress towards Phase III (year 3) tasks
Phase III (25-36 months)

Task 1-2. See Annual Report from collaborator Mohseni

Task 3. Analysis of anatomical connectivity patterns in rats after activity-dependent stimulation; Regulatory review and approval processes for non-human primate studies

Our original plan was to examine anatomical connectivity that could be altered by activity-dependent stimulation. However, the placement of the microelectrodes in the cerebral cortex interfered with the tract-tracing protocol, and, while we could demonstrate some connectivity, the anatomical data was not viable for quantitative analysis for comparison among groups. Also, as a result of an NIH-funded project in our laboratory investigating anatomical connectivity in a rat stroke model, we found that the normal rat connectivity patterns with the premotor area, that were a focus of our anatomical studies, are more diffuse than we found for non-human primates in earlier studies. Thus, the present anatomical experiment is somewhat underpowered for the quantitative analysis required. It will be necessary to propose a separate experiment to identify any anatomical changes, if they exist. We will submit a revised protocol requesting additional rats for this purpose to our local IACUC and subsequently, to ACURO during Year 4.

As a result of the *Nature* reviews, we focused on a more neurophysiological approach to determine connectivity between the target areas. This required no additional animals, but development of algorithms to analyze stimulus and spike timing events. The results of this analysis demonstrated conclusively that activity-dependent stimulation induces functional communication between the target areas, and is the basis for the functional recovery. These data were submitted in abstract form for the 2013 Society for Neuroscience meeting (appendix). Also, these data are part of the new manuscript in press in PNAS (Submitted and accepted, Year 4, Q1).

We also completed all review and approval processes for non-human primate studies. Approval has been obtained both from our local IACUC committee as well as ACURO. An on-site inspection of the KUMC facility by DoD was delayed by the budget sequestration, but will be re-scheduled as soon as it is convenient for the DoD representatives.

During Year 3, we also completed design of the plastic chambers that allow for internal mounting of the microdevice. The chambers are customized to fit the shape of the monkey skull. We then submitted plans for

fabrication, and received 20 chambers with lids. This was a collaborative effort between the neurobiological team at KUMC and the engineering team at Case Western Reserve University. We completed a pilot study in one squirrel monkey to verify that the monkey would tolerate the chamber mounted to the skull. Over the course of three months of wearing the chamber, there were no untoward effects, either with respect to the animal's health or well-being. As noted in previous communication with DoD, this was a separate pilot study required by our local IACUC prior to initiating the DoD studies, and thus, was funded by local sources. Since no DoD funding was used, it was approved by our local IACUC, but not submitted to ACURO.

Progress towards tasks from previous years

Phase I, Task 2. Rat optimization experiments in ketamine-anesthetized rats

While the initial goal of these experiments was the optimization of spike-stimulus delays, the rapid potentiation found with activity-dependent stimulation, but not open-loop stimulation, demonstrated that we can examine many parameters in anesthetized preparations relatively quickly. These experiments also showed that the functional connectivity changes are rather local. Potentiation was found only for the trigger electrode and a few electrode sites within 100 microns of the trigger electrode, but not more distant. These data were submitted in abstract for for the 2013 Society for Neuroscience meeting (appendix).

KEY RESEARCH ACCOMPLISHMENTS (within Year 3):

- Completed all regulatory requirements to continue study in non-human primates
- Analyzed functional connectivity data from rat study.
- Presented data at the 2012 Society for Neuroscience Annual Meeting (one symposium, one poster)
- Submitted abstracts to the 2013 Society for Neuroscience Annual Meeting (presented in November, 2013)
- Prepared manuscript for publication to be submitted to PNAS. (Submitted and accepted, Year 4, Q1)

REPORTABLE OUTCOMES:

1- Manuscripts/Abstracts/Presentations:

Peer-reviewed journal publications:

- Guggenmos, D.J., M. Azin, S. Barbay, J.D. Mahnken, C. Dunham, P. Mohseni and R.J. Nudo. Restoration of function after brain damage using a neural prosthesis. Major revisions including neurophysiological data analysis performed in Year 3. Submitted and accepted, *PNAS*, Year 4, Q1.

Abstracts:

- Guggenmos DJ, Azin M, Barbay S, Mahnken JD, Mohseni P, Nudo RJ (2012) Activity-dependent stimulation drives functional recovery after traumatic brain injury in the rat. Program No. 682.16. Society for Neuroscience Annual Meeting, 2012. Online.
- Guggenmos DJ, Dunham C, Azin M, Barbay S, Mahnken JD, Mohseni P, Nudo RJ Neurophysiological effects of activity-dependent stimulation following a controlled cortical impact to primary motor cortex of the rat. Society for Neuroscience Annual Meeting, 2013. Submitted during Year 3; presented in Year 4, Q1.
- Van Acker GM, Guggenmos D, Pack A, Dunham C, Nudo RJ Potentiating functional connectivity between distant cortical locations with activity dependent stimulation in the anesthetized rat. Program Society for Neuroscience Annual Meeting, 2013. Submitted during Year 3; presented in Year 4, Q1.

Oral presentations (Dr. Nudo):

- Invited Speaker, *Neuroprosthetic tools for repair of the injured brain*, annual Physical Medicine and Rehabilitation Conference, Cedars-Sinai Medical Center, Los Angeles, California, September 15, 2012.
- Invited Speaker, Symposium entitled "Hebb Recovers from a Stroke: Activity-Dependent Plasticity, Circuit Reorganization and Neural Repair in Cortex after Focal Ischemia", Society for Neuroscience Annual Meeting, October 15, 2012.
- Keynote Speaker, *Harnessing the potential of neuroplasticity to improve recovery after brain injury,* 33rd annual Braintree Neurorehabilitation Conference, Cambridge, Massachusetts, November 3, 2012.
- Invited Speaker, *Neuroprosthetic tools for repair of the injured brain*, Neurology Grand Rounds, Emory University, Atlanta, Georgia, November 16, 2012
- Invited Speaker, *Neuroprosthetic tools for repair of the injured brain*, Basic Neuroscience Seminar Series, University of Texas-Southwestern, Dallas, Texas, January 15, 2013.
- Invited Speaker, *The Emergence of Restorative Therapies: Drugs and Devices,* The Next Big Thing in Stroke (at Lightning Speed), Invited Symposium, American Heart Association International Stroke Conference, Honolulu, Hawaii, February 6, 2013.
- Invited Speaker, *Neuroprosthetic tools for repair of the injured brain*, LeFeber Winter Lecture Series on Aging, University of Texas Medical Branch, Galveston, Texas, April, 2013.
- Invited Speaker, *Neuroprosthetic tools for repair of the injured brain*, Spinal Cord and Brain Injury Research Center, niversity of Kentucky, Louisville, Kentucky, April, 2013.
- Keynote Speaker, *Neuroprosthetic tools for repair of the injured brain*, Third Rehabilitation Medicine Summit Forum, Beijing, China, August 10, 2013.

2- Patents and Licenses Applied for/Issued:

None issued yet.

3- Degrees Obtained from Award:

- David Guggenmos, PhD, Department of Molecular and Integrative Physiology (RJ Nudo, mentor), awarded June 2012

4- Development of Cell Lines and Tissue/Serum Repositories: Not applicable.

5- Informatics (Databases and Animal Models): None yet.

6- Funding Applied for: None yet.

7- Employment/Research Opportunities Applied for/Received: None yet.

CONCLUSION:

Rapid progress is being made toward developing smart prosthetic platforms for altering plasticity in the injured brain, leading to future therapeutic interventions for TBI that are guided by the underlying mechanisms for long-range functional and structural plasticity in the cerebral cortex. An unprecedented, potent effect of activity-dependent stimulation (ADS) on motor performance has been demonstrated in rats with TBI. Neurophysiological evidence suggests that functional connectivity between the target areas is enhanced by activity-dependent stimulation. Design of the device, and pilot experiments for non-human primates are underway.

REFERENCES:

None.

APPENDIX:

- Guggenmos, D.J., M. Azin, S. Barbay, J.D. Mahnken, P. Mohseni and R.J. Nudo. Restoration of function after brain damage using a neural prosthesis. Proceedings of the National Academy of Science, in press.
- Guggenmos DJ, Azin M, Barbay S, Mahnken JD, Mohseni P, Nudo RJ (2012) Activity-dependent stimulation drives functional recovery after traumatic brain injury in the rat. Program No. 682.16. Society for Neuroscience Annual Meeting, 2012. Online.
- Guggenmos DJ, Dunham C, Azin M, Barbay S, Mahnken JD, Mohseni P, Nudo RJ Neurophysiological effects of activity-dependent stimulation following a controlled cortical impact to primary motor cortex of the rat. Society for Neuroscience Annual Meeting, 2013. Submitted.
- Van Acker GM, Guggenmos D, Pack A, Dunham C, Nudo RJ Potentiating functional connectivity between distant cortical locations with activity dependent stimulation in the anesthetized rat. Program Society for Neuroscience Annual Meeting, 2013. Submitted.

Restoration of function after brain damage using a neural prosthesis

David J. Guggenmos[a,b,1], Meysam Azin[c,2], Scott Barbay[a,b], Jonathan D. Mahnken[d], Caleb Dunham[a,b], Pedram Mohseni[c], and Randolph J. Nudo[a,b,3]

Departments of [a]Molecular and Integrative Physiology and [d]Biostatistics, and [b]Landon Center on Aging, Kansas University Medical Center, Kansas City, KS 66160; and [c]Department of Electrical Engineering and Computer Science, Case Western Reserve University, Cleveland, OH 44106

Edited* by Michael Merzenich, Brain Plasticity Institute, San Francisco, CA, and approved November 15, 2013 (received for review September 6, 2013)

Neural interface systems are becoming increasingly more feasible for brain repair strategies. This paper tests the hypothesis that recovery after brain injury can be facilitated by a neural prosthesis serving as a communication link between distant locations in the cerebral cortex. The primary motor area in the cerebral cortex was injured in a rat model of focal brain injury, disrupting communication between motor and somatosensory areas and resulting in impaired reaching and grasping abilities. After implantation of microelectrodes in cerebral cortex, a neural prosthesis discriminated action potentials (spikes) in premotor cortex that triggered electrical stimulation in somatosensory cortex continuously over subsequent weeks. Within 1 wk, while receiving spike-triggered stimulation, rats showed substantially improved reaching and grasping functions that were indistinguishable from prelesion levels by 2 wk. Post hoc analysis of the spikes evoked by the stimulation provides compelling evidence that the neural prosthesis enhanced functional connectivity between the two target areas. This proof-of-concept study demonstrates that neural interface systems can be used effectively to bridge damaged neural pathways functionally and promote recovery after brain injury.

brain–machine–brain interface | neural plasticity | traumatic brain injury | closed-loop | long-term potentiation

The view of the brain as a collection of independent anatomical modules, each with discrete functions, is currently undergoing radical change. New evidence from neurophysiological and neuroanatomical experiments in animals, as well as neuroimaging studies in humans, now suggests that normal brain function can be best appreciated in the context of the complex arrangements of functional and structural interconnections among brain areas. Although mechanistic details are still under refinement, synchronous discharge of neurons in widespread areas of the cerebral cortex appears to be an emergent property of neuronal networks that functionally couple remote locations (1). It is now recognized that not only are discrete regions of the brain damaged in injury or disease but, perhaps more importantly, the interconnections among uninjured areas are disrupted, potentially leading to many of the functional impairments that persist after brain injury (2). Likewise, plasticity of brain interconnections may partially underlie recovery of function after injury (3).

Technological efforts to restore brain function after injury have focused primarily on modulating the excitability of focal regions in uninjured parts of the brain (4). Purportedly, increasing the excitability of neurons involved in adaptive plasticity expands the neural substrate potentially involved in functional recovery. However, no methods are yet available to alter the functional connectivity between spared brain regions directly, with the intent to restore normal communication patterns. The present paper tests the hypothesis that an artificial communication link between uninjured regions of the cerebral cortex can restore function in a rodent model of traumatic brain injury (TBI). Development of such neuroprosthetic approaches to brain repair may have important implications for the millions of individuals who are left with permanent motor and cognitive impairments after acquired brain injury, as occurs in stroke and trauma.

For the present experiment, we used a rodent model of focal brain injury to the caudal forelimb area (CFA), a region that is part of the cortical sensorimotor system. This area in the frontal cortex shares many properties with primary motor cortex (M1) of primates; injury to M1 results in long-term impairment in reaching and grasping functions (5). Traditionally, it has been thought that impairment occurs because M1 provides substantial outputs to the motor apparatus in the spinal cord, thus directly affecting motor output function. However, M1 also has important interconnections with the primary somatosensory cortex (S1) located in the parietal lobe (Fig. 1*A*). Long-range corticocortical fibers from S1 provide critical information to M1 about the position of the limb in space. Thus, injury to M1 results in impaired motor performance due, at least in part, to disruption in communication between the somatosensory and motor cortex (6).

To test our hypothesis that functional recovery can be facilitated by creating an artificial communication link between spared somatosensory and motor regions of the brain, we focused on the rat's premotor cortex (PM). The rostral forelimb area (RFA) is a premotor area in the rodent's frontal cortex that shares many properties with PM of primates and is thought to participate in recovery of function after injury to M1 (5, 7–9). PM areas are so-named because the principal target of their output fibers is M1 (10). PM areas also have long-range corticocortical connections with somatosensory areas, but at least in

Significance

Closed-loop systems, or brain–machine–brain interfaces (BMBIs), have not been widely developed for brain repair. In this study, we targeted spared motor and somatosensory regions of the rat brain after traumatic brain injury for establishment of a functional bridge using a battery-powered microdevice. The results show that by using discriminated action potentials as a trigger for stimulating a distant cortical location, rapid recovery of fine motor skills is facilitated. This study provides strong evidence that BMBIs can be used to bridge damaged neural pathways functionally and promote recovery after brain injury. Although this study is restricted to a rodent model of TBI, it is likely that the approach will also be applicable to other types of acquired brain injuries.

Author contributions: D.J.G., M.A., P.M., and R.J.N. designed research; D.J.G., M.A., and S.B. performed research; D.J.G., M.A., J.D.M., C.D., P.M., and R.J.N. analyzed data; and D.J.G., M.A., J.D.M., P.M., and R.J.N. wrote the paper.

The authors declare no conflict of interest.

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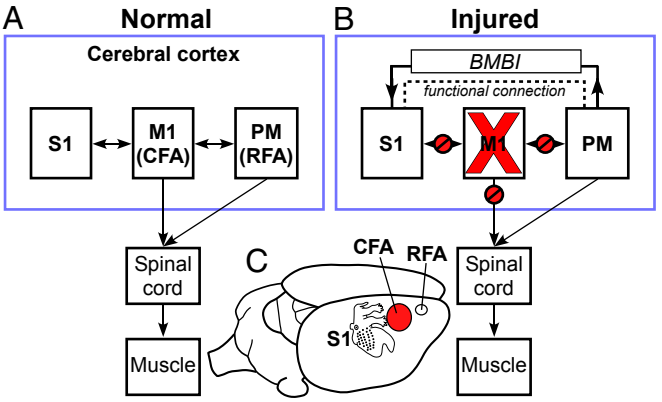

Fig. 1. Theoretical model of neuroprosthetic treatment approach after brain injury. (*A*) Normal connectivity of M1, S1, and PM. Both M1 (CFA in rat) and PM (RFA in rat) send substantial outputs to the spinal cord via the corticospinal tract. Also, extensive reciprocal connections exist between M1 and PM, as well as between M1 and S1. (*B*) Effects of focal M1 injury on brain connectivity and the hypothetical effect of a BMBI to restore somatosensory-motor communication. An injury to M1, as might occur in stroke or brain trauma, results in a focal area of necrosis, as well as loss of M1 outputs to the spinal cord. Corticocortical communication between M1 and S1 (and between M1 and PM) is also disrupted, further contributing to functional impairment. Because the uninjured PM also contains corticospinal neurons, it might have the ability to serve in a vicarious role. The dotted line indicates enhanced functional connection between PM and S1 that we propose is established after treatment with a BMBI. (*C*) Location of target areas in rat cerebral cortex. A topographic map of the somatosensory representation in S1 is superimposed on the cortex.

intact animals, they appear to be relatively weak compared with M1's connections with the somatosensory cortex (9, 11, 12).

Our approach was to link the neural activity of the PM forelimb area (RFA) functionally with activation of the S1 forelimb area following a controlled cortical impact (CCI) to M1 (Fig. 1 *B* and *C*). To this end, a microdevice was developed with the ability to deliver activity-dependent stimulation (ADS) through recording and digitizing extracellular neural activity from an implanted microelectrode, discriminating individual action potentials (spikes), and delivering small amounts of electrical current to another microelectrode implanted in a distant population of neurons (13, 14). This closed-loop system was similar, in principle, to the "Neurochip" used previously by other investigators to demonstrate the effects of local ADS in intact animals (15), but it was miniaturized for head-mounted, wireless operation (Fig. 2*A* and Fig. S1). By linking the activity of one area of the cortex with that of a distant area of the cortex, a closed-loop brain–machine–brain interface (BMBI) for artificial corticocortical communication between PM and S1 was created.

Individual spikes were detected in PM, and subsequent stimulation was delivered to S1 after a 7.5-ms delay (Fig. 2*B*). (Because connections between distant cortical areas are commonly reciprocal, enhanced communication theoretically could be established by ADS in either direction.) After the M1 injury, rats were implanted with microelectrodes connected to the BMBI microdevice (Fig. 2*A*). The microdevice delivered ADS 24 h per day up to 28 d postinjury, except for brief motor assessment sessions on predetermined days. Behavioral recovery in ADS rats was compared with recovery in rats with open-loop stimulation (OLS), in which S1 stimulation was uncorrelated with spikes in PM, and with control rats that had no microdevice implanted.

Results

Testing Motor Skill After Brain Injury. The primary behavioral assay for determining whether ADS resulted in functional improvement after brain injury was a skilled reaching task. This widely used task is a particularly sensitive measure of forelimb motor function after M1 lesions in both rodents and primates. Rats were pretrained to achieve a minimum criterion score of >70% successful pellet retrievals. After the lesion was created, rats were tested on the task during assessment sessions on postlesion days 3, 5, 8, 14, 21, and 28. During each postlesion assessment session, rats were tested under two conditions: first with the microdevice stimulation function turned OFF and then with the stimulation function turned ON. Rats in each of the three groups demonstrated a severe deficit on the skilled reaching task in the first few days after the injury (Fig. 3). On postlesion days 3 and 5, there were no significant differences in motor performance between the groups (global comparisons: $P = 0.5265$ and $P = 0.0945$, respectively). Rats in the control group (with a lesion but no microdevice) continued to demonstrate a profound deficit that plateaued at only about 25% successful retrievals. In striking contrast, by postlesion day 8, group performance was significantly different (global comparison: $P = 0.0044$). Rats in the ADS group showed a substantial and statistically significant behavioral improvement in reaching success compared with rats in the other groups in the ON condition (pairwise comparisons: $P = 0.0418$ for ADS vs. OLS, $P = 0.0012$ for ADS vs. control, and $P = 0.2110$ for OLS vs. control; Fig. 3 and Movies S1 and S2). By postlesion day 14, the performance of the rats in the ADS group was approximately at prelesion levels and significantly higher than that of rats in the other groups. The difference between the OLS group and the control group approached significance on day 14 (global comparison: $P = 0.0004$; pairwise comparisons: $P = 0.0284$ for ADS vs. OLS, $P < 0.0001$ for ADS vs. control, and $P = 0.0555$ for OLS vs. control). By postlesion day 21, performance in the ADS group remained high and statistically different from that of the control group. Performance was not significantly different in the ADS group between days 14 and 21 ($P = 0.576$). However, by day 21, the OLS group had improved further, so that the difference between the two groups was not significant (global comparison: $P = 0.0007$;

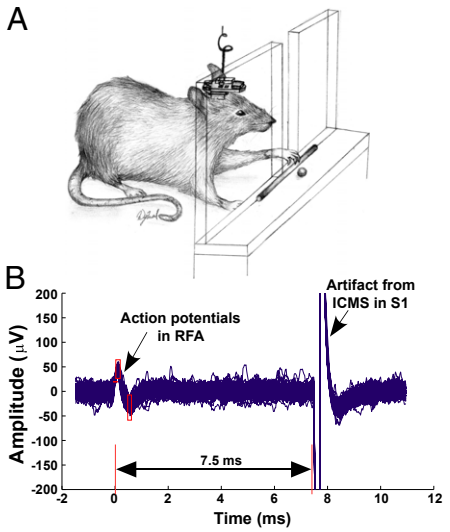

Fig. 2. ADS protocol. After injury to the CFA, a recording microelectrode was placed in the RFA, whereas a stimulating microelectrode was placed in the distal forelimb field of S1. A BMBI discriminated action potentials in the RFA, and after a 7.5-ms delay, it delivered a low-level electrical current pulse to S1 (13). (*A*) Sketch of a rat retrieving a food pellet with a BMBI attached to the skull. (*B*) Sample traces of recordings from the RFA showing action potentials and stimulus artifacts from an ICMS current delivered to S1. Time-amplitude window discriminators are indicated by red boxes. A total of 100 superimposed traces are shown.

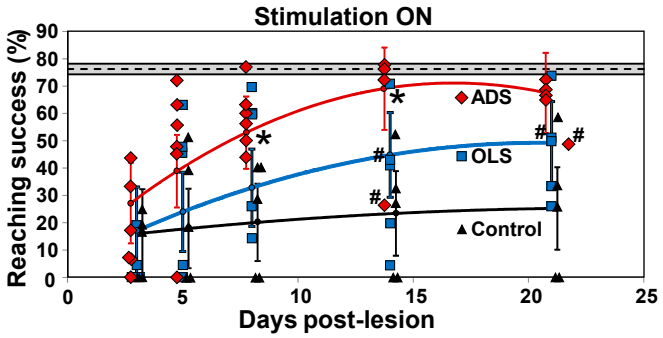

Fig. 3. Performance of rats on a skilled reaching task after injury to M1 (ON condition). The ADS group is shown in red, the OLS group is shown in blue, and the control group is shown in black. The dotted line indicates the average prelesion performance of all animals in the study. The bounded area indicates the 95% confidence interval. Regression lines are based on an LMM (43). Error bars represent 95% confidence intervals. *$P < 0.05$ (pairwise difference between the ADS and OLS groups). Because the statistical analysis was an intent-to-treat model, rats were included in the analysis even if the microdevice was no longer functional. Only one rat in the ADS group had a microdevice that was functional by postlesion day 28; thus, figures are presented through postlesion day 21 (*SI Results*). Diamonds, squares, and triangles represent individual animal data points. #, microdevice not functional (Tables S1 and S2).

pairwise comparisons: $P = 0.0891$ for ADS vs. OLS, $P = 0.0002$ for ADS vs. control, and $P = 0.0278$ for OLS vs. control). Although the mean performance of the ADS group was higher than that of the OLS group even in the OFF condition, differences were not statistically significant on any postlesion day (Fig. S2).

Immediate Effects Within Single Sessions. Rats in the ADS group often showed substantially improved performance within a single day's session when the microdevice was switched from the OFF to the ON condition. One particularly salient example can be seen in a video of a rat in the ADS group on postlesion day 8 (Movie S2). In the OFF condition, this rat made many attempts to reach through the opening in the Plexiglas but was rarely able to do so accurately. Large trajectory errors were made, and relatively few retrievals were completed successfully. Following completion of trials in the OFF condition, the microdevice was programmed to the ON state, a process that required 2–3 min. As soon as the microdevice was turned ON, the rat began to retrieve pellets with noticeably enhanced success. Movements tended to be slower and seemingly more deliberate, and fewer errors were made. A statistical analysis of the ADS group between the OFF and ON conditions revealed significantly better performance in the ON condition on postlesion day 3 ($P = 0.0003$), postlesion day 5 ($P = 0.0005$), and postlesion day 8 ($P = 0.0019$) and marginally better performance on postlesion day 14 ($P = 0.0666$). The same analysis for the OLS group revealed significantly worse performance in the ON condition on postlesion day 3 ($P = 0.0471$) and marginally worse performance on postlesion day 5 ($P = 0.0554$) and postlesion day 8 ($P = 0.0781$) (Fig. S3). These effects tended to dissipate over time, so that no differences were detected between OFF and ON conditions in either group by postlesion day 21. These within-day differences through postlesion day 8 suggest that the timing of the S1 stimulus pulse is critical. Behavioral performance was significantly better when the S1 stimulus pulse was delivered contingent upon an action potential in the RFA (i.e., in the ADS group).

Effects of ADS on Functional Connectivity. To explore possible neurophysiological mechanisms underlying the behavioral effects of the ADS treatment on postinjury motor performance, we performed post hoc analysis of spike events in the RFA that were discriminated in the 28 ms after each S1 stimulus pulse. This time window represented our imposed blanking period during which additional S1 stimulus pulses could not occur. Poststimulus spike histograms were compared with 28-ms periods chosen from data acquired in the OFF condition 7.5 ms after each RFA spike event. The results show that substantially more spikes in the RFA occurred following S1 stimulation in the ADS group, with peak activity occurring ~4–6 ms after the S1 stimulus pulse (Fig. 4*A*). Spike rates were nearly threefold higher averaged across the 28-ms period compared with a comparable period in the OFF condition. Spike rates in the OLS group were slightly lower than in the ADS group in the OFF condition but were significantly lower than in the ADS group in the ON condition. These data suggest that ADS substantially reinforced network interactions between S1 and the RFA, whereas OLS did not.

Subdividing the spike histograms by day reveals that enhanced spike activity in the ADS ON condition is evident even on the first day that the microdevice was activated (Fig. 4*B* and Fig. S4). There is also a trend toward further increases in spike discharge between the first (days 1 and 5) and second (days 8 and 14) weeks in the ADS group, corresponding to the time period when behavioral performance approached normal levels.

Whether behavioral performance and enhanced functional connectivity persist following the end of treatment cannot be addressed fully based on the current results (*SI Discussion*). However, it is noteworthy that there was a significant decrease in mean performance in the ADS group between postinjury days 21 and 28 (Fig. S5). During this time period, microelectrode-microdevice connection failures prevented normal operation of the microdevice in most of the ADS rats. This phenomenon of reduced behavioral performance after deactivation provides further

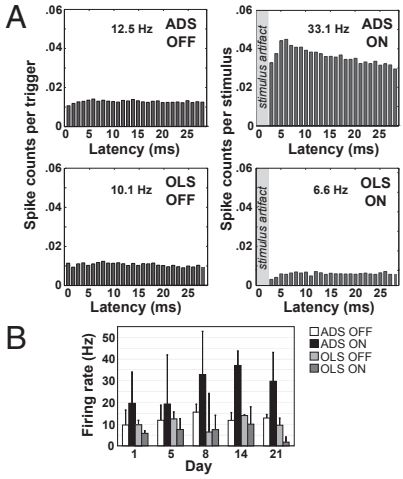

Fig. 4. Comparison of spike activity in the RFA in the ADS and OLS groups. Data represent spikes discriminated in the RFA over a 28-ms period. In the ON condition, the trigger for the data acquisition was the S1 stimulus pulse. In the OFF condition, the trigger for the data acquisition was 7.5 ms after a spike event in the RFA. (*A*) Composite posttrigger spiking histograms derived from neural recordings in the RFA compiled from days 1, 5, 8, 14, and 21 (±1 d). Histograms portray the mean spike counts per trigger event within each time bin (also Fig. S4). Spike counts were based on an average of over 22,000 trigger events per animal per day. Poststimulus firing rates were substantially higher in the ADS ON condition (33.1 Hz), compared with the ADS OFF (12.5 Hz), OLS ON (6.6 Hz), or OLS OFF (10.1 Hz) condition. (*B*) Average spike firing rates throughout the 28-ms window for each day. Error bars represent between-subject variation on each day (plus 1 SD). LMMs detected higher firing rates in the ADS group compared with the OLS group with stimulation ON ($P < 0.0001$). Firing rates did not differ statistically between groups in the OFF condition ($P > 0.05$). Posttrigger spiking histograms for each day are shown in Fig. S4.

support for the notion that the behavioral improvements were mediated by closed-loop operation. It also suggests that either a longer duration of operation (i.e., beyond 21 d) is required for persistent effects or that closed-loop stimulation enhances the rate, but not the extent, of recovery compared with OLS. Nonetheless, the present data provide persuasive evidence that targeted closed-loop stimulation approaches are feasible as brain repair strategies. Rapid behavioral recovery parallels the development of increased functional connectivity between spared somatosensory and motor regions of the cortex.

Discussion

This proof-of-concept study indicates that a closed-loop neuroprosthetic microdevice can enhance functional connectivity between distant cortical locations and generate rapid improvement in motor function after cortical injury, at least in rats with M1 damage. A closed-loop device with similar functionality induced neurophysiological changes when applied over a short distance within M1 of intact monkeys (15). More recently, spike-triggered stimulation was used to demonstrate increased potentiation between neurons in the sensorimotor cortex of rats. The spike-stimulation delay was important, because 5 ms resulted in robust increases, whereas 100 or 500 ms resulted in no potentiation (16). The present study demonstrates that the extension of the ADS approach to injured brains has demonstrable effects on recovery and establishes functional communication that is qualitatively different compared with uncorrelated stimulation. The current implementation of the system architecture, using a lightweight, battery-powered, wireless, miniaturized microdevice for spike-triggered intracortical microstimulation (ICMS), represents an important step in the process of developing implantable BMBIs for neural repair in clinical populations.

Differential Mechanisms Underlying the Effects of OLS and ADS on Behavioral Recovery. The mechanisms underlying the therapeutic effects of OLS and ADS after injury in the present model of TBI are still somewhat speculative. In the 1940s, Donald Hebb (17) postulated that "When one cell repeatedly assists in firing another, the axon of the first cell develops synaptic knobs… in contact with the soma of the second cell." This hypothesis has morphed into the modern maxim "Cells that fire together, wire together," a phrase made popular by neuroscientist, Carla Shatz (18). A large literature has grown from these initial hypotheses, and a neurophysiological phenomenon widely known as "Hebbian plasticity" has formed the basis for many neuroscientific models of learning and memory. Previous studies in intact primates and rodents using ADS or paired-pulse stimulation show the ability for such coactivation to alter output properties of cortical neurons (15, 16, 19). Presumably, the stimulation causes Hebbian-like plasticity to alter existing connectivity within a cortical area.

Although significant behavioral recovery occurred in both the ADS and OLS groups compared with control rats, the ADS group improved substantially more rapidly. Also, in the early postlesion period, the ADS group demonstrated a qualitatively different ON vs. OFF performance compared with the OLS group. These behavioral results alone suggest that different mechanisms underlie recovery in ADS and OLS groups. Although the results of ICMS on behavioral outcomes in animal models of brain injury have not been reported previously, several studies have examined the therapeutic effects of surface stimulation in either human stroke survivors or animal stroke models. For example, an invasive technology using epidural stimulation to provide low-level current pulses over uninjured cortical areas during the execution of rehabilitative training resulted in behavioral improvement in rodent and nonhuman primate models of cortical ischemic injury (20, 21). Although initial results in clinical stroke populations were promising, the therapeutic effect of open-loop epidural stimulation was not demonstrated in a randomized clinical trial (22). Nonetheless, noninvasive cortical stimulation approaches (transcranial magnetic stimulation and transcranial direct-current stimulation) continue to attract substantial interest due to positive results in small groups of stroke survivors (23).

Evidence to support specific mechanisms underlying the effects of open-loop electrical stimulation of the cortex on recovery is largely correlative but includes motor map reorganization, increased dendritic length and spine density, cell proliferation and cell migration in the subventricular zone, receptor subunit expression, activation of antiapoptotic cascades, increased neurotrophic factors, enhanced angiogenesis, and proliferation of inflammatory cells (20, 21, 24–28). Because the number of stimulus pulses was similar in the ADS and OLS groups in the present study, it is reasonable to conclude that if electrical stimulation promoted proliferative processes, the effects were the same in the two groups.

In addition, various OLS protocols produce alterations in synaptic efficacy. These data are particularly relevant because of the qualitative differences in functional connectivity observed between ADS and OLS groups. Long-term potentiation (LTP), an experimental phenomenon first discovered in the hippocampus of anesthetized rabbits over 40 y ago (29), is expressed in both excitatory and inhibitory synapses throughout the mammalian brain (30). Although many experimental protocols have been developed to optimize synaptic potentiation in various model systems, the sign and magnitude of synaptic potentiation are heavily dependent upon the frequency and pattern of stimulation (31, 32).

Despite comparable mean stimulation frequency between the two groups, the temporal structure of stimulus pulses differed between the ADS and OLS groups. Interstimulus intervals spanned approximately the same range, but the intrinsic temporal firing pattern observed in the ADS group resulted in a greater number of short interstimulus intervals (Fig. S6*A*). Thus, ADS stimulation occasionally consisted of stimulus pulses at higher frequency, somewhat analogous to theta-burst stimulation, in which train bursts of high-frequency pulses (e.g., four to eight pulses at 100–300 Hz) are delivered at about 6–7 Hz (i.e., within the theta-rhythm frequency). Theta-burst stimulation is often used to optimize generation of LTP, especially in the neocortex of awake animals, where LTP has traditionally been more difficult to generate (33). In a study in the neocortex of freely moving rats, theta-burst stimulation, using parameters similar to those used in the hippocampus, evoked LTP, but the effects required at least 5 d to develop and plateaued at about 15 d (34). In the present study, although enhanced, short-latency spike discharge was evident with ADS even on the first day of stimulation, the time course of the behavioral effects was remarkably similar to the slowly developing LTP found in the rat neocortex study.

Theta-burst timing protocols vary considerably depending upon the particular model system. However, a recent study in a mouse brain slice preparation in the dorsal striatum suggests that the optimal theta-burst patterns are those that best match intrinsic neural activity patterns (35). Further, "burstiness" was critical to inducing LTP. Simply reducing the interburst pause from 35 ms to 20 ms eliminated the induction of LTP. It is possible that our imposed 28-ms blanking period further contributed to the neurophysiological and behavioral effects. We propose that by using a closed-loop stimulation paradigm, the intrinsic stimulation patterns that optimally drive synaptic potentiation in the cortico-cortical pathways were used. (The feasibility of using optimal theta-burst parameters in an open-loop mode of stimulation is discussed in *SI Discussion*).

In summary, OLS and ADS may both contribute to behavioral recovery but by somewhat different mechanisms. Electrical stimulation, in general, is likely to modulate neuronal growth processes, leading to adaptive plasticity that could account for at least part of the behavioral improvement. In the closed-loop (ADS) condition, however, the intrinsic firing pattern drives synaptic

potentiation in a manner similar to that observed in theta-burst protocols. Although potentiation builds rapidly (within 1 d), we propose that chronic ADS results in a behaviorally relevant, functional connection between S1 and PM.

Future Applications of Closed-Loop Neuroprostheses for Treating Neurological Disorders. A closed-loop neuroprosthesis applying ADS across distant cortical areas is a vastly different approach to brain repair than has been achieved to date. Therapeutic closed-loop stimulation in the brain is still uncommon. However, analogous approaches are already being tested for epilepsy, and an expanded role for closed-loop systems for deep brain stimulation in Parkinson disease is now being considered (36, 37). Further, closed-loop approaches are under development in animal models of spinal cord injury (38, 39). Other investigators have proposed a closed-loop approach for a cognitive prosthesis that has shown promise in animal models (40). Other potential clinical applications based on the current model include stroke, focal TBI, and surgical resections. Finally, a variety of neurological syndromes that are thought to be related to disruption of cortical communication may be amenable to ADS. In the 1960s, Norman Geschwind identified several disorders collectively called "disconnection syndromes," revolutionizing the field of behavioral neurology (41). The consideration of closed-loop approaches to repair of cortical disconnection syndromes may open treatment options for a variety of conditions in which neural communication is disrupted, whether due to disease, injury, or idiopathic causes.

Materials and Methods

Animals. Adult, male Long–Evans hooded rats (n = 16, weight: 350–450 g; Harlan) were procured at 4 mo of age. Protocols for animal use were approved by the Kansas University Medical Center Institutional Animal Care and Use Committee and adhered to the *Guide for the Care and Use of Laboratory Animals* (42). Each rat was singly housed in a transparent cage and provided with food and water ad libitum. The room was kept on a 12-h:12-h light/dark cycle, and ambient temperature was maintained at 22 °C.

Rats were assigned to three groups: the ADS group, the OLS group, and the control group. Rats in all three groups received a CCI injury over the M1 forelimb area (5). Postmortem histological analysis confirmed that lesion size was comparable across groups (*SI Results*). The surgical procedures (e.g., burr holes, skull screws, dura resection) were identical in all three groups. Microelectrode implantation and microdevice attachment were identical in the ADS and OLS groups. In both the ADS and OLS groups, one single-shank microelectrode array was inserted into the S1 forelimb area. A second single-shank microelectrode array was inserted into the RFA (depths are provided in *SI Materials and Methods*). In the ADS group, stimulation in S1 was contingent upon spike activity in the RFA; that is, time-amplitude window discriminators determined when action potentials were recorded from the RFA microelectrode. Discrimination of an individual action potential triggered delivery of a brief pulse of electrical current to the microelectrode implanted in S1. In the OLS group, the stimulation was delivered arbitrarily at a frequency approximately the same as that in the ADS group but with the timing of stimulation uncorrelated with the discriminated action potentials (*SI Materials and Methods*). The wireless, battery-powered microdevice, mounted to the freely moving rat's skull, operated 24 h per day (Fig. 2*A* and Fig. S1).

CCI Procedure. In each rat, the skull over the CFA was removed while leaving the dura intact. A 3-mm diameter rod with a flat tip was placed into a commercial impactor device (Leica Microsystems), centered over the target location (*SI Materials and Methods*), and then lowered until the surface of the tip was in contact with the dura, as indicated by an audible signal triggered by a feedback sensor. The rod was then retracted and armed. An impact was delivered with an excursion of 2 mm below the surface of the dura. This protocol leads to reproducible lesions that damage all cortical layers within the CFA with minimal superficial damage to underlying white matter tracts and limited or no damage to adjacent cortical areas (5).

Microdevice Programming. ***ADS programming.*** To determine discrimination parameters for ADS, the channel with the best signal-to-noise ratio was chosen. This same channel was later used during microdevice operation to determine spike events that triggered stimulation. Using a custom MATLAB (MathWorks) script, action potentials were discriminated offline by thresholding and two user-adjustable time-amplitude windows, with the intent of maximizing discrimination of observed spikes while minimizing noise and/or stimulus artifacts. Stimulation parameters were set to deliver a 60-μA, 192-μs, pseudobiphasic current pulse with a 7.5-ms delay following spike discrimination (Fig. 2*B*). A blanking interval following each spike discrimination prevented additional stimulus pulses for 28 ms. The spike discrimination, timing, and stimulation parameters were then uploaded to the microdevice for online spike discrimination. Thus, during device operation in the ADS group, each discriminated spike in PM triggered a stimulation pulse in S1, constrained by the blanking interval.

The 7.5-ms delay was based on previous studies of the effective delay within local networks, analysis of spike-stimulus delays in pilot data, as well as constraints in the current microdevice architecture. The 28-ms blanking interval was also based on analysis of spike-stimulus delays in pilot data and was set to reduce the possibility of producing a positive-feedback loop, in which S1 stimulation might drive action potentials in PM, retriggering stimulation of S1.
OLS programming. Stimulation parameters were the same in the OLS group as for the ADS group. However, the stimulation was not contingent upon recorded neural activity. Instead, the stimulation was set to occur arbitrarily with interstimulus intervals ranging from 35 to 200 ms (randomized equally across the range), closely approximating the stimulus rate for the ADS group (*SI Materials and Methods*, *SI Results*, and Fig. S6*A*).
Signal monitoring and maintenance. The neural activity and stimulation rates were monitored daily throughout the study via a wireless connection. The microdevice ran continuously, delivering ADS or OLS 24 h a day during the experiment, except for brief periods required for behavioral assessment, changing the battery, and adjusting the window discriminator parameters.

Bandpass-filtered neural data (~500 Hz to 5 kHz) were recorded at ~35.7 kHz per channel from either one or four channels (wireless or wired connection, respectively) during all signal monitoring and behavioral trials using LabVIEW software (National Instruments). In addition, all animals had multiple sessions during which data were recorded during home cage behavior. The raw signal recording duration of any single monitoring period was software-limited to ~45 min, but the stimulus trigger signal could be recorded for up to 24 h. The neural signal data were converted from a LabVIEW file to a text file and analyzed using custom MATLAB software.

Behavioral Training and Assessment. ***Skilled reaching task.*** Each rat was tested in a 30-cm × 30-cm × 52-cm Plexiglas reaching chamber. For each trial, a single food pellet (45 mg; Bioserv) was placed into a shallow well 2 cm from the front wall on an external shelf positioned 3 cm from the bottom of the chamber. The rat was required to reach through a narrow slot to retrieve the pellet with its forepaw (Fig. 2*A*). After forelimb preference was determined, a removable Plexiglas wall was used to force the animal to use only the preferred forelimb (5). Trials were recorded with a digital camcorder for playback and analysis. The percentage of success was measured as the percentage of trials in which the rat grasped, retrieved, and brought the pellet to the mouth (60 trials per day). Before entry into the remainder of the study, the rat was required to reach and retrieve food pellets above 70% success for 3 consecutive days. Following the injury (see below), behavioral probing sessions were conducted on postlesion days 3, 5, 8, 14, 21, and 28. Testing on postlesion days 1 and 2 was not practical due to the effects of surgical recovery and postsurgical analgesics on behavioral performance. Probing sessions consisted of 20 trials with the microdevice stimulation function turned OFF and then 20 trials with the microdevice stimulation function turned ON.
Foot-fault task. Rats were also assessed on a foot-fault task to determine the effects of the injury on a locomotion task. In general, although there was an effect of the injury on this task on postlesion day 3, no lesion effects were observed on subsequent days. Also, there were no differences between groups at any time points. This result was not unexpected, because the foot-fault task is less sensitive, and spontaneous recovery is common with lesions restricted to the forelimb motor cortex.

Statistical Analysis of Behavioral Performance. Initially, animals were randomly assigned to an ADS (n = 6) or control (n = 5) group. A subsequent OLS group (n = 5) was studied after group randomization. This was necessary to use neurophysiological data from the ADS group to determine the stimulation protocol for the OLS group.

Linear mixed models (LMMs) (43) were generated via restricted maximum likelihood estimation using SAS version 9.2 PROC GLIMMIX (SAS Institute, Inc.) to model performance on the skilled reaching task for each animal over time. Results are presented to mirror a series of one-way ANOVA models because the LMM provides analogous results. For animals in the ADS and

OLS groups, the difference between the OFF and ON conditions was studied as an outcome. Models included fixed effects for treatment group, time, and their interaction.

Time was treated as a continuous measure to generate estimates of a polynomial relationship for recovery profiles in each treatment group over time up to a (treatment group-specific) quadratic relationship. Animal-specific effects were introduced by allowing for random intercepts in these models; thus, the models allowed for estimation of normally distributed error terms both for between- and within-animal effects. Backward elimination was used to determine the functional form of these relationships with F test P values <0.05 for effects to remain in the models. All lower ordered terms were retained in models in the presence of higher level interaction effects, regardless of statistical significance. Models were evaluated by visual inspection of observed vs. predicted values for each animal to assess model fit, observed vs. residuals plots to assess constant variance assumptions, and histograms of the residuals and quantile-quantile plots to assess the assumption of normally distributed random effects. Residuals included both those for the random intercept coefficients (for between-animal error terms) and overall residuals (for within-animal error terms).

Linear contrasts of model estimates were used to test for treatment group differences on postlesion days 3, 5, 8, 14, 21, and 28 using F tests, with day 28 serving as the a priori time point of interest for the comparison of ADS vs. OLS. Other pairwise comparisons at each time point were also tested (*SI Materials and Methods*, *Protocol Deviations*). Given the single, a priori primary comparison, no further adjustments for multiple comparisons were made. Linear contrasts were used to generate 95% confidence intervals for each treatment group for those specific days and, within the ADS and OLS groups, to test for differences in the OFF vs. ON conditions. Two-sided P values were used for presentation of results.

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NEUROSCIENCE 2012

Presentation Abstract

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Presentation Title: Activity-dependent stimulation drives functional recovery after traumatic brain injury in the rat

Location: Hall F-J

Presentation time: Tuesday, Oct 16, 2012, 4:00 PM - 5:00 PM

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Abstract: Traumatic brain injury (TBI) affects nearly 1.6 million Americans annually. These injuries can lead to severe cognitive and physical deficits, but there are few available treatments that can promote functional recovery. Following an injury to primary motor cortex (M1), not only does extensive cell loss occur in the core of the injury, but widespread denervation of spared cortical areas in the sensorimotor network occurs as well. This disruption of somatosensory and motor integration contributes significantly to the severity of the motor deficit. The aim of this study was to use activity-dependent stimulation (ADS) following cortical TBI to M1 in order to create an artificial communication link between spared pre-motor cortex and primary somatosensory cortex (S1). Our hypothesis was that the artificial link would promote functional recovery on a skilled motor task. To produce ADS between the two areas, a wireless microdevice was developed to record, filter and digitize neural activity, utilize on-device real-time spike detection, and deliver time-locked stimulation pulses to a distant electrode. The microdevice acts as a closed-loop brain-machine-brain interface for syncing neural activity between areas in frontal and parietal cortex. In this study, rats were given a controlled cortical impact (CCI) over the forelimb area of primary motor cortex (caudal forelimb area, CFA) to simulate a TBI. Immediately following injury, a recording microelectrode was placed in the spared pre-motor cortex (rostral forelimb area, RFA) and a stimulating microelectrode into the hand area of S1. The microdevice was connected to the electrodes, and generated ADS 24 hours a day for up to 28 days. Behavioral recovery from the CCI was assessed during the study using a

skilled reaching task. Statistical analysis using a linear mixed model demonstrated that animals that received the ADS (n=6) showed significant recovery compared to non-stimulated, injured controls (n=5) and animals receiving randomized (open-loop) stimulation to S1 (n=5). The results from this study demonstrate that reestablishing communication between spared sensory and motor areas can drive functional behavioral recovery following a TBI.

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Keyword(s): TRAUMATIC BRAIN INJURY

PLASTICITY

MOTOR CORTEX

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Neuroscience 2013

Presentation Abstract

Program#/Poster#: 79.12/VV10

Presentation Title: Neuroelectrophysiological effects of activity-dependent stimulation following a controlled cortical impact to primary motor cortex of the rat

Location: Halls B-H

Presentation time: Saturday, Nov 09, 2013, 4:00 PM - 5:00 PM

Topic: ++D.18.b. Neurophysiology: Implanted electrodes, other direct interactions with neurons

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Abstract: Following a unilateral injury to primary motor cortex (M1), reorganization in spared motor cortical areas is thought to restore some of the lost functionality resulting from the lesion. Further, disruption of sensorimotor integration influences the severity of motor deficit. Previously, we have shown that recovery of function following M1 injury in a rat model of traumatic brain injury is enhanced by establishing an artificial sensorimotor communication link between the spared rostral forelimb area (RFA, a premotor area) and the forepaw area of the primary somatosensory cortex (S1). This approach used activity-dependent stimulation (ADS) to artificially link the two areas. Detection of action potentials (spikes) in RFA triggered electrical stimulation in S1 to promote Hebbian plasticity. In the present study, we sought neurophysiological evidence that communication between RFA and S1 was altered by ADS. Rats were given a traumatic brain injury by controlled cortical impact (CCI) over the forelimb area of M1. The animals were then implanted with recording electrodes in RFA and stimulating electrodes in S1. A wireless, battery-operated, custom-built microdevice was then attached to the electrodes and set to deliver either activity-dependent stimulation (ADS, N=6) or randomized, open-loop stimulation (OLS, N=5) up to 24 hours daily for 28 days following the CCI. Stimulation parameters were such that detected spikes in PM would trigger a single 200µs pseudo-biphasic 60µA stimulation pulse in S1 after a

7.5ms delay. A 28ms blanking period from initial detection of the spike provided a fixed time window to observe evoked neural activity in RFA following the S1 stimulation pulse. Both groups received similar amounts of stimulation (ADS = 8.26Hz ± 3.86Hz; OLS = 8.18Hz ± 1.42Hz) and had similar inter-spike intervals. ADS, but not OLS, led to a change in the firing rate of the neurons recorded in RFA used to trigger the stimulation. That is, in the ADS group, but not the OLS group, there was a significant increase in spikes in RFA in the 28ms following the S1 stimulation pulse compared to periods when the stimulation was off ($p < 0.0001$). The increase in stimulus-evoked spikes was observed within hours upon the initiation of ADS, and persisted for the duration of the experiment (up to 28 days). Taken together with the previous behavioral results, these data demonstrate that following a lesion to M1, communication between two distant areas (RFA and S1) can be facilitated using ADS, and that this artificial communication link aids in recovery. This demonstration may have substantial implications in development of closed-loop therapeutic interventions following cortical injury.

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RAT

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